

REMARKS

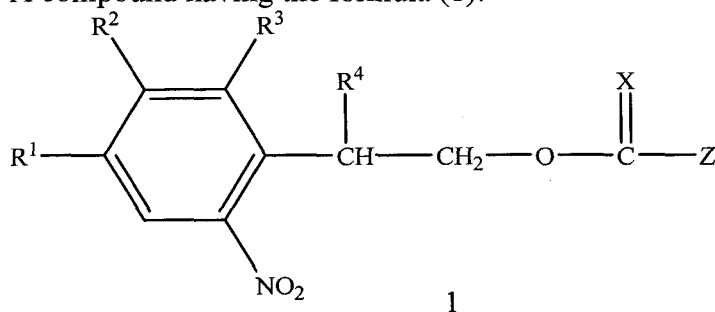
Claims 1 and 3-46 are pending in the present application.

The rejection of Claim 1 under 35 U.S.C. §102(e) over Pan et al is respectfully traversed.

On page 6 of the Office Action, the Examiner alleges that Pan et al disclose a compound mentioned anticipates the compound of formula (1) in Claim 1, wherein R<sup>1</sup> is H, R<sup>2</sup> an optionally substituted aryl group, R<sup>3</sup> is a halogen, R<sup>4</sup> is H, X is O, and Z is a leaving group. Applicants disagree with this allegation by the Examiner.

Applicants remind the Examiner that Claim 1 provides:

A compound having the formula (1):



wherein

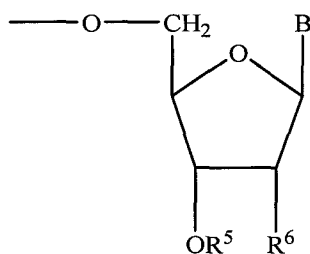
R<sup>1</sup> is selected from the group consisting of H, NO<sub>2</sub>, CN, OCH<sub>3</sub>, a halogen, an optionally substituted alkyl having up to 4 carbon atoms, and an optionally substituted alkoxyl having up to 4 carbon atoms, under the proviso that R<sup>2</sup> is selected from the group consisting of an optionally substituted aryl group, an optionally substituted heteroaryl group and an optionally substituted aroyl group;

R<sup>3</sup> is selected from the group consisting of H, NO<sub>2</sub> and a halogen;

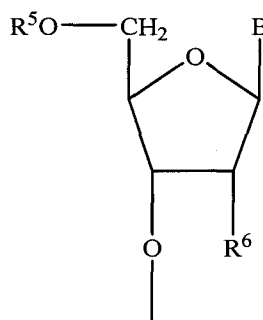
R<sup>4</sup> is selected from the group consisting of H, OCH<sub>3</sub> and an optionally substituted alkyl group having up to 4 carbon atoms;

X is selected from oxygen or sulfur; and

Z is selected from the group consisting of a leaving group, an alcohol, an O-atom of an hydroxyl group and a N-atom of an amine group, respectively, of a compound comprising the photolabile protective group, or a deoxyribonucleoside or a ribonucleoside as represented by either of the following formulae (2) or (3):



2



3

wherein

R<sup>5</sup> is selected from the group consisting of a H, an oligonucleotide and a functional group useful in oligonucleotide synthesis;

R<sup>6</sup> is selected from the group consisting of H, OH, an optionally substituted alkoxyl having up to 4 carbon atoms, and an optionally substituted alkenoxyl group having up to 4 carbon atoms, or WR<sup>8</sup> wherein W is selected from oxygen and sulfur and R<sup>8</sup> is selected from a protective group useful in oligonucleotide synthesis;

B is base selected from the group consisting of adenine, cytosine, guanine, thymine, uracil and chemical modifications thereof and in the case of adenosine, cytosine and guanine the amino functions on the heterocycle may bear a protective group useful in oligonucleotide synthesis; or

Z is selected from the group consisting of a chemically modified deoxyribonucleoside, a chemically modified ribonucleoside, and an analog thereof.

It is clear from the plain language of Claim 1 that R2 is an aryl group that may be substituted. This is further supported by the specification at page 11, lines 15-21, which define the term "aryl" as follows:

The term "aryl", alone or in combination with any other term, refers to a carbocyclic aromatic radical, preferably consisting of from 6-14 carbon atoms, and more preferably consisting of from 6-10 carbon atoms. Examples of aryl radicals include, but are not limited to phenyl, naphthyl, indenyl, indanyl, azulenyl, fluorenyl, anthracenyl and the like. Aryl radicals may be optionally substituted with 1 to 3 substituents selected from the group including, but not limited to alkyl, alkoxy, halogen, hydroxyl, amino, acyl, nitro, cyano, thioalkyl and the like.

Thus, viewed with the foregoing, when the aryl group is substituted, the aryl group of R2 is directly bonded to the phenyl group of formula (I). In other words, a biphenyl structure is claimed (with a C-C bond).

In contrast, Pan et al disclose aminopyridyl-substituted phenyl acetamides with a C-N bond which are quite different from our biphenyl compounds of Claim 1. Thus, Pan et al do not anticipate the claimed invention.

Applicants request withdrawal of this ground of rejection.

The rejection of Claims 30, 31, 35-39, 45, and 46 under 35 U.S.C. §102(b) over Eritja et al, is respectfully traversed.

The Examiner alleges that the aforementioned claims are anticipated by Eritja et al. To this end, the Examiner alleges that compound 9 of Eritja et al corresponds to the claimed compounds of Claims 30, 31, 40, and 41 wherein R1 is COOY and Y is an alkyl group up to 10 carbons, R2 is H and R3 is H. Applicants disagree with this allegation by the Examiner.

The primary difference between Claim 30 of the present application and Eritja et al is at R4. According to Claim 30, R4 is "selected from the group consisting of OCH<sub>3</sub> and an optionally substituted alkyl group having up to 4 carbon atoms". In Eritja et al, the position corresponding to R4 is H.

The Examiner appears to recognize this deficiency in the disclosure of Eritja et al, but attempts to side-step this deficiency by alleging "the definition of R4 "up to 4 carbon atoms" includes zero carbon atoms as well". Applicants respectfully submit that this allegation is completely without merit and finds no scientific support.

The feature "an alkyl group having up to 4 carbon atoms" means that the alkyl group must have 1 to 4 carbon atoms. An alkyl group with zero carbon atoms simply does not exist.

Accordingly, Applicants submit that the Examiner's interpretation of pending Claim 30 is incorrect. Since Eritja et al fail to disclose all the limitations of the claimed invention, this reference cannot anticipate the claimed invention.

Furthermore, the corresponding protective groups according to Eritja et al are cleaved off by the treatment of basic compounds in organic solvents. In contrast, the protective groups according to the present invention are cleaved off by photolysis.

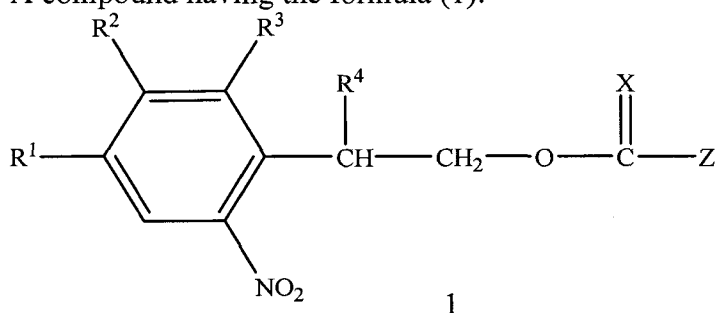
In view of the foregoing, Applicants request withdrawal of this ground of rejection.

The: (a) rejection of Claims 30-46 under 35 U.S.C. §103(a) over US 5,763,599 (Pfleiderer et al), and (b) the obviousness-type double patenting rejection of Claims 30-46 over Claims 1-14 of US 5,763,599 (Pfleiderer et al), are respectfully traversed.

The Examiner alleges that Pfleiderer et al disclose and claim compounds that are covered by the genus of compounds set forth in Claim 30, as well as positional isomers of the claimed compounds. Applicants respectfully disagree.

Claim 30 of the present application provides:

A compound having the formula (1):



wherein

$R^1$  is COOY, wherein Y is selected from the group consisting of an optionally substituted alkyl group of up to 10 carbon atoms, under the proviso that  $R^2$  is selected from the group consisting of H, NO<sub>2</sub>, CN, OCH<sub>3</sub>, a halogen, an optionally substituted alkyl having up to 4 carbon atoms, and an optionally substituted alkoxy having up to 4 carbon atoms;

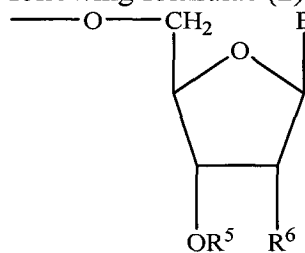
$R^3$  is selected from the group consisting of H, NO<sub>2</sub> and halogen;

$R^4$  is selected from the group consisting of OCH<sub>3</sub> and an optionally substituted alkyl group having up to 4 carbon atoms;

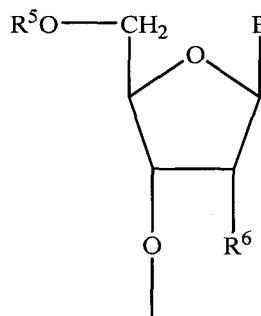
X is selected from oxygen or sulfur; and

Z is selected from the group consisting of a leaving group, an alcohol, an O-atom of an hydroxyl group and a N-atom of an amine group, respectively, of a compound comprising the photolabile protective group,

or a deoxyribonucleoside and a ribonucleoside as represented by either of the following formulae (2) or (3):



2



3

wherein

R<sup>5</sup> is selected from the group consisting of a H, an oligonucleotide and a functional group useful in oligonucleotide synthesis;

R<sup>6</sup> is selected from the group consisting of H, OH, an optionally substituted alkoxyl having up to 4 carbon atoms or an optionally substituted alkenoxyl having up to 4 carbon atoms, or WR<sup>8</sup> wherein W is selected from oxygen and sulfur and R<sup>8</sup> is selected from a protective group useful in oligonucleotide synthesis;

B is base selected from the group consisting of adenine, cytosine, guanine, thymine, uracil and chemical modifications thereof and in the case of adenosine, cytosine and guanine the amino functions on the heterocycle may bear a protective group useful in oligonucleotide synthesis; or

Z is selected from the group consisting of a chemically modified deoxyribonucleoside, a chemically modified ribonucleoside, and an analog thereof.

Notable in Claim 30, and contrary to the compounds disclosed and claimed in Pfleiderer et al, compounds of this claim differ with regard to the substituents at the R1 position from the compounds of Pfleiderer et al. According to Claim 30 of the present application R1 is COOY, wherein Y is selected from the group consisting of an optionally substituted alkyl group up to 10 carbon atoms, under the proviso that R2 is selected from the group consisting of H, NO<sub>2</sub>, CN, OCH<sub>3</sub>, a halogen, an optionally substituted alkyl having up to 4 carbon atoms and an optionally substituted alkoxy having up to 4 carbon atoms.

In contrast, the substituent at the R1 position according to Pfleiderer et al is H, NO<sub>2</sub>, CN, OCH<sub>3</sub>, halogen or alkyl or alkoxy alkyl having 1 to 4 C atoms. At no point is a COOY substituent mentioned at all by Pfleiderer et al.

Applicants direct the Examiner to *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) in which the Court of Appeals for the Federal Circuit clearly state that in order to find a *prima facie* case of unpatentability, a showing that the “prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention” was also required (*Takeda* at 1174, citing *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990); *In re Grabiak*, 769 F.2d 729, 226 USPQ 870 (Fed. Cir. 1985); *In re Lulu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984)).

Moreover, as clearly stated by *Takeda* at 1174, the Court squarely addressed the test for *prima facie* obviousness enunciated by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 [82 USPQ2d 1385](2007) in the context of chemical compounds:

That test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.<sup>2</sup> While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation(“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does” in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is “no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis.” *Id.* As long as the test is not applied as a “rigid and mandatory” formula, that test can provide “helpful insight” to an obviousness inquiry. *Id.* Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.*** (*emphasis added*)

In view of the foregoing, Applicants submit that the present invention is not obvious in view of Pfleiderer et al as this reference fails to provide the requisite reason that would have led a chemist to modify the compounds disclosed therein in the manner necessary to arrive at the claimed compounds. Thus, Pfleiderer et al fails to support even a *prima facie* case of obviousness, which would also preclude a holding of obviousness-type double patenting.

Moreover, the compounds of the present application show unexpected results as compared to the compounds of Pfleiderer et al. The protective groups according to the present invention can be cleaved off by photolysis in a much better manner.

Again, Applicants submit that with respect to Claim 30, it should be noted that Pfleiderer et al merely discloses compounds in which R<sup>1</sup> (nomenclature according to the present application) is equal to H, OCH<sub>3</sub>, NO<sub>2</sub> or CN. In contrast, the compounds according to the new Claim 30 require R<sup>1</sup> to be COOY. Such compounds are not disclosed in Pfleiderer et al. Therefore, Claim 30 is novel in view of Pfleiderer et al. Moreover, Pfleiderer et al offers no motivation to modify their disclosed compounds to arrive at the compounds as presently claimed in Claim 30 (and the claims dependent therefrom). Accordingly, the disclosure and the claims of Pfleiderer et al fail to render the claimed invention in Claim 30 (and the claims dependent therefrom) obvious.

Also as stated above for Pfleiderer et al, in Claim 30 of the present application R<sup>1</sup> is equal to COOY. In contrast, R<sup>1</sup> (designation in Pfleiderer et al = R<sup>3</sup>) is H, Cl or OCH<sub>3</sub>.

Further, with respect to Claim 1<sup>1</sup>, Applicants submit that Pfleiderer et al exclusively disclose compounds in which R<sup>2</sup> (nomenclature according to the present application) is equal to H or OCH<sub>3</sub>. In contrast, the compounds in pending Claim 1 require that R<sup>2</sup> is an optionally

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<sup>1</sup> Claim 1 is discussed in this section since the Examiner references Claim 1 of the present application on page 5 of the Office Action mailed September 13, 2007.

substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted aroyl group. No compounds meeting this requirement are disclosed in Pfleiderer et al. Therefore, Claim 1 is novel in view of Pfleiderer et al. Moreover, Pfleiderer et al offers no motivation to modify their disclosed compounds to arrive at the compounds as presently claimed in Claim 1 (and the claims dependent therefrom). Accordingly, the disclosure and the claims of Pfleiderer et al fail to render the claimed invention in Claim 1 (and the claims dependent therefrom) obvious.

Tables 1 to 4 on pages 51 to 53 of the present application contain a *direct* comparison of the inventive protective groups with a protective group according to Pfleiderer et al. The protective group designated as compound No. 26 in the present application corresponds to compound 10 in Pfleiderer et al.

For the case of cleaving the protective groups off by photolysis – both in solution and under dry conditions - Tables 1 to 4 of the present application show that the inventive protective groups whose radical  $R^2$  differs from those of Pfleiderer et al have half lives that are one half or only one third as long as those of the protective groups of Pfleiderer et al. This proves that the deprotection time has been accelerated by a factor of 2 to 3 compared with Pfleiderer et al by the introduction of an aromatic radical at  $R^2$ .

Table 5 of the present application shows that 86% yields were attained after as little as 18 seconds even in the dry system by using a protective group (Bz-NPPOC) modified at  $R^2$  in the manner of the invention. In contrast, the NPPOC protective group, compound 10 of Pfleiderer et al (see compound 36 of Hasan et al, submitted on December 15, 2006) led only to 81% conversion after 65 seconds. This proves the considerable technical advance of the new protective groups containing a specific  $R^2$  radical.

Not only during deprotection under dry conditions and during deprotection in solution

but also during deprotection in support-bound systems. Therefore, the protective groups of the present application exhibit much faster deprotection times than do those from Pfleiderer et al.

More directly relevant to the Examiner's current allegations with respect to Claims 30-46, proof that the protective groups according to Claim 30 of the present application containing  $R^1 = \text{COOY}$  also bring about a considerable technical advance compared with Pfleiderer et al can be seen by referring to Fig. 3 of the present application. Accordingly, a protective group according to Claim 30, in which  $R^1$  was changed compared with Pfleiderer et al and deprotected by irradiation under dry conditions, or in other words without solvent, exhibits a much improved yield. The protective groups compared in Fig. 3 include, among others, 5'-MeC-NPPOC-dt (according to Claim 30 of the present application) and 5'-NPPOC-dT (corresponds to Pfleiderer et al). Fig. 3 shows that the inventive 5'-MeC-NPPOC-dt protective group leads to a deprotection yield of 82% after as little as 20 seconds, whereas never more than a 57% deprotection yield could be achieved even after 1 minute with the protective group from Pfleiderer et al (5'-NPPOC-dT). Thus the protective group according to Claim 30 not only is better in deprotection time but also is drastically better in absolute deprotection yield.

A comparable experiment with a support-bound protected desoxythymidine (see Fig. 5 of the present application) yielded 85% conversion after 11 seconds in the case of the inventive t-BuC-NPPOC-dT (compound 25), whereas comparable conversion could be achieved with non-inventive MeNPOC-dT (prior art protective group) only after 29 seconds.

Figs. 3 and 5 as well as Tables 1 to 5 therefore show that the inventive protective groups containing radicals  $R^1$  or  $R^2$  (nomenclature according to the invention) changed by comparison with Pfleiderer et al represent a considerable technical advance in photolysis in a

dry system. This technical advance is manifested by much higher yields accompanied at the same time by much shorter half lives.

Tables 1 to 4 of the invention show further that the inventive protective groups modified at  $R^2$  also exhibit a considerable technical advance compared with Pfleiderer et al during photolyses in solution.

Starting from Pfleiderer et al as the closest prior art, the objective problem of the present application must be regarded as providing protective groups that can be cleaved off more rapidly and at the same time lead to higher yields, especially in the dry system.

The solution of this problem, or in other words the introduction of COOY groups at  $R^1$  or of aromatic groups at  $R^2$ , is based on careful deliberations and is not made obvious by Pfleiderer et al.

Thus Hasan et al (see reference filed December 15, 2006, which has the same content as Pfleiderer et al, but provides somewhat more accurate and more extensive information on the properties of the compounds disclosed in Pfleiderer et al) discloses on page 4251, lines 2 to 3 that it is particularly important for the photolytic cleaving off of protective groups to introduce a suitable substituent on the  $\alpha$ -C atom – corresponding to  $R^4$  in claims 1 and 29 of the present application. In an additional requirement according to Hasan et al, page 4250, last paragraph, it is important to introduce a suitable substituent in o-position on the ring.

In regard to substituents in the m- and p-positions on the ring of formula 1, Hasan et al, page 4247, Abstract, last sentence, teaches that ***“In general, substitutions at other positions on the phenyl ring had less effect on photolysis rates.”*** According to Hasan et al, page 4250, lines 1 to 2, these results are in agreement with other scientific investigations.

In summary, it therefore follows from Hasan et al that the substituents at  $R^4$  or in o-position on the ring must be optimized, and *that changes at  $R^1$  and  $R^2$  have no positive effect*

(see Hasan et al, page 4247, Abstract, last sentence).

Against this background and the unequivocal teaching from Hasan et al, it was *not* obvious to introduce new substituents at R<sup>1</sup> and R<sup>2</sup>. To the contrary, Hasan et al even leads *away* from the present application, since it imparts to the person skilled in the art the impression that he must vary R<sup>4</sup> (in claim 1) or the o-position in the ring. He therefore would not have seen any “reasonable expectation of success” by varying the R<sup>1</sup> or R<sup>2</sup> position.

But even if this had not been taken into consideration, there is no kind of indication in Pfleiderer et al or Hasan et al as to what type of change, or in other words which substituents, must be introduced at R<sup>1</sup> and R<sup>2</sup> position in order to improve the effectiveness of photolytic cleavage of protective groups. The radicals R<sup>1</sup> and R<sup>2</sup> used according to claim 1 are not made obvious by Pfleiderer et al or Hasan et al.

In summary, Pfleiderer et al fails to render the present invention obvious. Accordingly, Applicants request withdrawal of this ground of rejection.

Finally, Applicants note that this response addresses all grounds of rejection raised in the Office Action mailed September 13, 2007. Some rejections raised in the Office Action mailed September 15, 2006, have not been referenced in either the Rejections Withdrawn section (pages 2-3 of the Office Action mailed September 13, 2007) or the section setting forth outstanding rejections (pages 3-9 of the Office Action mailed September 13, 2007). Thus, it is Applicants understanding that all rejections not specifically indicated as being outstanding have been withdrawn. If this is not the case, then the next action setting forth any new grounds of rejection should be a *non-final* action, especially in view of the fact that no amendments have been made in the present response.

Applicants respectfully submit that the above-identified application is now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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